

The Action of Nitrils  
ON  
Substituted Organic Acids

BY  
August Henry Gotthelf.

Submitted in Partial Fulfilment of the Requirements  
for the Degree of Doctor of Philosophy in  
the Faculty of Pure Science,  
Columbia University.

NEW YORK, 1900.

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# THE ACTION OF NITRILS ON SUBSTITUTED ORGANIC ACIDS.

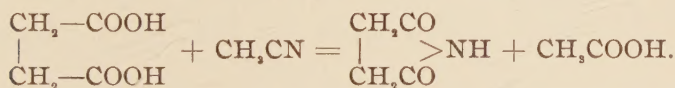
## PART I.

### THE ACTION OF ALIPHATIC NITRILS ON $\beta$ -SULPHOPROPIONIC AND *o*-SULPHOBENZOIC ACIDS.

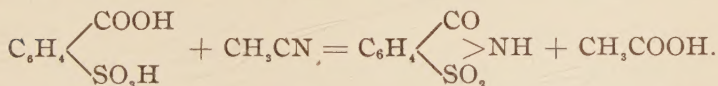
#### INTRODUCTION.

The following work is a continuation of investigations already carried out in this laboratory on the reactions occurring between acids and nitrils when heated under pressure.

The first systematic experiments on this subject were made by Colby and Dodge.<sup>1</sup> Miller<sup>2</sup> and Seldner,<sup>3</sup> working with succinic and glutaric acids, respectively, obtained results having especial bearing on this part of my work. They found that the action of acetonitril on these acids gave their imids according to the following equation :



These experiments with dibasic acids were continued by Mathews,<sup>4</sup> who worked particularly with acids of the aromatic series. Among others he used *o*-sulphobenzoic acid, hoping to obtain saccharin by a reaction similar to the above :



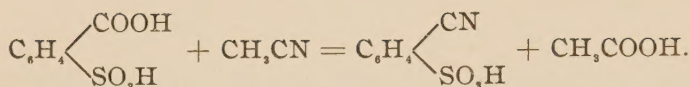
Another possible reaction was a simple interchange of the COOH and CN groups, giving *o*-sulphobenzonitril, an isomer of saccharin.

<sup>1</sup> Am. Chem. J., 13, 1.

<sup>2</sup> J. Am. Chem. Soc., 16, 443.

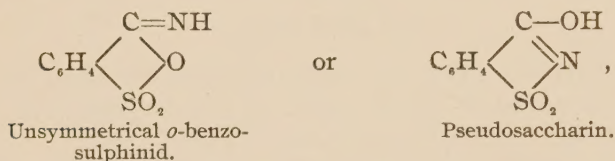
<sup>3</sup> Am. Chem. J., 17, 532.

<sup>4</sup> J. Am. Chem. Soc., 20, 654.



This, as found by Colby and Dodge, is the usual reaction between monobasic aromatic acids and aliphatic nitrils.

Mathews, however, obtained a body having the same percentage of nitrogen as saccharin, but entirely different in properties from both the latter and *o*-sulphobenzonitril. He concluded that it might be one of the other possible isomers of saccharin, *viz.*,



but was unable, for lack of time, to do much work on it.

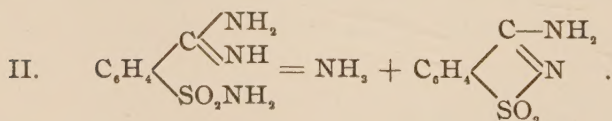
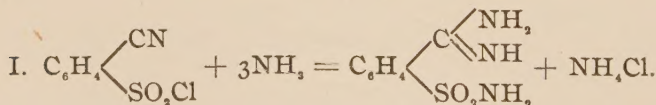
I have repeated his experiments, and, in addition, have tried the same reaction with  $\beta$ -sulphopropionic acid, hoping to obtain a body of a similar constitution.

To my knowledge, neither the compound itself nor derivatives of unsymmetrical *o*-benzosulphinid are known.

Derivatives of pseudosaccharin were first made by Jesurun.<sup>1</sup>

Pseudosaccharinamid,  $\text{C}_6\text{H}_4 \begin{array}{l} \diagup \text{C-NH}_2 \\ \diagdown \text{N} \\ \text{SO}_2 \end{array}$ , was prepared by the

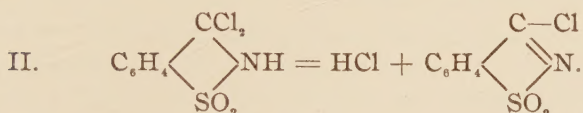
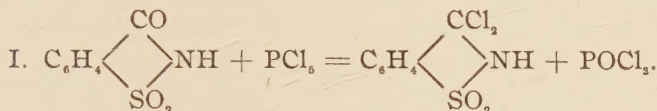
action of the theoretical quantity of ammonia on *o*-cyanbenzolsulphochloride :



<sup>1</sup> Ber. d. chem. Ges., 26, 2286.



Pseudosaccharin chloride,  $\text{C}_6\text{H}_4\begin{array}{c} \text{C}-\text{Cl} \\ \diagup \quad \diagdown \\ \text{N} \\ \diagdown \quad \diagup \\ \text{SO}_2 \end{array}$ , was obtained by treating saccharin with  $\text{PCl}_5$  at  $180^\circ$  under atmospheric pressure.



By means of this chloride Jesurun succeeded in making ethers and other derivatives. All attempts to prepare pseudosaccharin itself failed, saccharin being formed in every instance.

The results of my work on this subject have been most unsatisfactory. From the reaction with  $\beta$ -sulphopropionic acid I obtained nothing definite. That with *o*-sulphobenzoic acid gave apparently the same body that Mathews had worked with, but analysis indicates that it is not isomeric with saccharin. As the yield is at best small and purification difficult I was unable to obtain very much of it and failed to determine its constitution.

#### EXPERIMENTAL WORK.

##### 1. $\beta$ -Sulphopropionic Acid and Acetonitril.

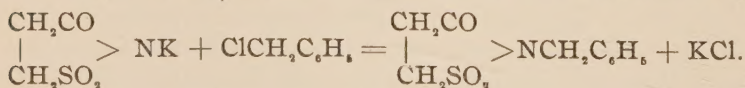
The  $\beta$ -sulphopropionic acid was prepared by the method of Rosenthal.<sup>1</sup>  $\beta$ -iodopropionic acid is dissolved in water and ammonium carbonate added until the solution is neutral. Ammonium sulphite is then added and the whole boiled for several hours. The ammonium salts present are then decomposed with baryta water and all ammonia driven out, the barium is precipitated with carbonic acid gas, the solution filtered, and the barium carbonate precipitate repeatedly extracted with hot water, as it tends to hold back much of the barium sulphopro-

<sup>1</sup> Ann. Chem. (Liebig), 233, 16.

pionate. The combined filtrates are then evaporated to a small bulk and, on cooling, the barium sulphopropionate crystallizes. After one or two recrystallizations this salt will be quite pure, when it is weighed, dissolved in warm water and decomposed with the exact amount of a standard sulphuric acid solution. The barium sulphate is filtered out and the filtrate evaporated until the acid remains as an oily liquid, which solidifies in an evacuated desiccator to a light brown crystalline mass melting at  $68^{\circ}$ – $69^{\circ}$ . It is pulverized and dried and preserved in a desiccator over sulphuric acid.

*Tube 1.*—This was made up of equal molecules of the acid and acetonitril with a few drops of acetic anhydride. It was heated first to  $150^{\circ}$  for five hours. At the end of this time there was no pressure, and the tube contents consisted of a white crystalline substance and a thick brown fluorescent liquid. An amount of acetonitril equal to that already present was added and the tube heated to  $175^{\circ}$  for six hours. There was now less of the solid substance, otherwise the contents were the same as before. On heating to  $200^{\circ}$ – $205^{\circ}$  for three and one-half hours, all the solid had disappeared; there was slight pressure and an odor of acetic acid. The contents were poured into a dish and heated on the water-bath to drive off acetonitril, acetic acid, etc. The residue was a brown, viscous liquid, which was soluble in alcohol and water, less soluble in chloroform, and insoluble in ether and benzol. Attempts to obtain crystals from it by various solvents failed. On boiling with caustic alkali, ammonia was evolved. On dissolving in water and adding barium chloride and caustic potash, a slight precipitate was obtained, containing no nitrogen, which was probably barium sulphopropionate.

An attempt was made to obtain a benzyl ether of any imid that might be present, according to the following equation:



The liquid was dissolved in alcohol and caustic potash and benzyl chloride added in the cold, but no potassium chloride separated.

*Tube 2.*—This also contained equal molecules of acid and nitril and was heated to  $150^{\circ}$  for four hours and then to  $200^{\circ}$  for another four hours. At the end of this time all of the crystals already noted in the first tube had not disappeared. On heating the contents on the water-bath as before, these crystals remained unmelted, showing that they were not unchanged  $\beta$ -sulphopropionic acid (m. p.  $69^{\circ}$ ). They were separated mechanically and were found soluble in alcohol, and insoluble in toluol, benzol, gasoline, acetone, chloroform, carbon disulphide, and acetonitril. They melted at about  $160^{\circ}$ ; after recrystallization from alcohol and acetone at about  $180^{\circ}$ . On boiling with caustic alkali, ammonia was given off. No precipitate was obtained with barium chloride directly but, after boiling with caustic potash, one was obtained.

*Tube 3.*—In this the proportions used were two molecules of nitril to one of acid, and it was heated first to  $150^{\circ}$  for three and one-half hours and then to  $250^{\circ}$ , when it exploded.

*Tube 4.*—This was made up of equal molecules and was heated successively to  $100^{\circ}$ ,  $120^{\circ}$ ,  $140^{\circ}$ , and  $175^{\circ}$  for two hours each, and finally to  $190^{\circ}$ – $200^{\circ}$  for six hours, when there was a strong pressure of sulphur dioxide in the tube and the contents were considerably carbonized. After heating on the water-bath to get rid of sulphurous and acetic acids, the product was extracted with hot water, which dissolved everything but a small carbonaceous residue. This extract was neutralized with barium carbonate, causing much effervescence and a precipitate, which, on filtering and recrystallizing, was found to contain barium, but no nitrogen, and proved to be barium sulphopropionate. The filtrate from the precipitate, which evolved ammonia on boiling with caustic alkali, was evaporated to a residue partly liquid on the water-bath and smelling of acetamid. Treatment with benzol removed this odor, but on evaporating the benzol solution to identify the acetamid only a trace of material was obtained. After this extraction the residue was treated with ninety-five per cent. alcohol, which dissolved all but a little white powder, which contained barium and no nitrogen, and was probably some more barium sulphopropionate. The alcoholic solution gave ammonia with caus-



tic alkali. It was evaporated to small bulk, but on standing in a desiccator for a long time it still remained semifluid, though showing a tendency to crystallize. This residue reddened litmus and decomposed carbonates, and was soluble in alcohol and water, and insoluble in benzol, acetone, and chloroform.

*Tube 5.*—This was also made up of equal molecules and heated exactly like tube 4.

It was attempted to extract acetamid directly with benzol, but none was found. The tube contents were then treated just as in No. 4, *i. e.*, extracted with hot water, barium carbonate added, the precipitate filtered out, and the filtrate evaporated to a semifluid residue. On standing, some colorless crystals were observed to form and these were separated mechanically and washed quickly with cold water, in which they were not very soluble. They contained sulphur, but no nitrogen.

The residue from which these crystals had been removed, was dissolved in absolute alcohol, the solution bone-blackened, and evaporated. A small crystalline residue was left which, on recrystallizing from absolute alcohol, gave colorless crystals melting at  $180^{\circ}$ – $181^{\circ}$ ; probably the same substance as that obtained from tube 2. It contained both sulphur and nitrogen, evolving ammonia with caustic alkali. Thinking the substance might be ammonium sulphopropionate, it was dissolved in water and barium chloride solution added, but no precipitate of barium sulphopropionate was obtained. The crystals were strongly acid toward litmus and decomposed carbonates, but too little was obtained for any further tests. The fact that they were acid though the first solution was neutralized with barium carbonate, would seem to indicate that they were the product of some secondary reaction, due to the later treatment.

*Tube 6.*—This contained the same proportions as tube 5, but was heated only to  $165^{\circ}$ – $170^{\circ}$  for two hours. The product consisted of a fluorescent syrup containing some colorless crystals and smelling of acetic acid. It was extracted with cold absolute alcohol, by which the crystals were left undissolved; they melted at  $185^{\circ}$  and were apparently the same as those obtained from tube 5.

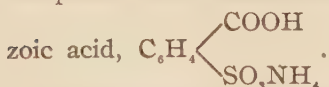
The alcoholic solution was bone-blackened, evaporated, and placed in a desiccator. After a time, some micaceous crystals separated, which melted at about  $125^{\circ}$  and contained sulphur and nitrogen. They were soluble in acetone; insoluble in gasoline, chloroform, and benzol. On boiling with baryta water (evolving ammonia), passing carbonic acid gas to precipitate the excess of barium and filtering the solution hot, no barium sulphopropionate separated from the filtrate on cooling.

*Tube 7.*—The contents and temperature were exactly like No. 6. On treating with absolute alcohol a little more of the substance melting at  $181^{\circ}$ – $184^{\circ}$  was obtained. The alcoholic solution, on evaporation and standing in a desiccator, again deposited micaceous crystals, which, on recrystallizing from 95 per cent. alcohol, also melted at  $183^{\circ}$ – $184^{\circ}$ . The crystals obtained from tube 6, melting at  $125^{\circ}$ , appear, therefore, to have been but an impure form of the substance already found, melting at  $183^{\circ}$ – $184^{\circ}$ .

The yield of anything at all definite from these tubes being exceedingly poor and uncertain, experiments with  $\beta$ -sulphopropionic acid were abandoned and those with *o*-sulphobenzoic acid taken up.

## 2. Experiments with *o*-Sulphobenzoic Acid.

An easy method of making *o*-sulphobenzoic acid and the one used by both Mathews and myself is that of Remsen.<sup>1</sup> Saccharin is boiled with concentrated hydrochloric acid which decomposes it and forms the acid ammonium salt of *o*-sulphoben-



This is quite easily soluble in water and can thus be separated by filtration from insoluble *p*-sulphamine benzoic acid which may also be present in the saccharin. The crystallized ammonium salt is then treated with phosphorus pentachloride at the ordinary temperature until action has ceased, forming the chlorides,



<sup>1</sup> Am. Chem. J., 11, 332.

The mixture is poured into ice-water where the chlorides separate as a heavy yellow oil, which, after thorough washing, is boiled with water to form *o*-sulphobenzoic acid. On evaporation the acid crystallizes with 4 molecules of water in long needles, melting at  $68^{\circ}$ ; to obtain it anhydrous it is necessary to heat to  $130^{\circ}$ – $135^{\circ}$  (the melting-point of the anhydrous acid), for some time and preserve it in an evacuated desiccator over sulphuric acid. The acid gradually darkens during the heating and a constant weight could not be obtained.

*a. Action of Acetonitril on o-Sulphobenzoic Acid.*—Tubes containing equal molecular proportions of acid and nitril were heated to  $165^{\circ}$ – $195^{\circ}$  for three to seven hours. It was found that a temperature of  $165^{\circ}$ – $170^{\circ}$  for three to five hours gave the best results; there was then no pressure in the tube and the contents consisted of a varying quantity, usually small, of crystalline material covered by a light brown syrup.

The crystals were believed by Mathews to be the acid ammonium salt of *o*-sulphobenzoic acid, and, on applying the following tests, I found them to be, in fact, that salt.

1. The substance contains both nitrogen and sulphur and melts at  $256^{\circ}$ – $260^{\circ}$ .

2. It is unchanged by boiling with concentrated hydrochloric acid.

3. Ammonia easily dissolves it, and, on acidifying, it is reobtained.

4. The barium and silver-ammonium salts of *o*-sulphobenzoic acid were prepared from it by the method of Remsen and Dohme.<sup>1</sup> The barium salt was made by boiling the substance in aqueous solution with barium carbonate until no more ammonia was evolved, filtering, and evaporating the filtrate. The salt crystallized in handsome clusters of white needles just as described. On ignition it formed barium sulphate.

The silver-ammonium salt was made similarly by boiling with freshly precipitated silver oxide, filtering and evaporating. Crystals were obtained containing silver, turning brown above  $130^{\circ}$ , and otherwise as described.

The tubes were all treated in the following manner: The

<sup>1</sup> Am. Chem. J., 11, 336.



contents were extracted with absolute alcohol, which dissolved everything but the acid ammonium salt. This solution was then bone-blackened, evaporated to a very small bulk, and placed in an evacuated desiccator to crystallize. The crystals seldom separated until almost all of the alcohol had evaporated, leaving them imbedded in a light brown syrup. After trying various solvents the best method for their separation was found to consist in treating them with acetonitril, which dissolved the syrup but left the crystals untouched. Then, on recrystallizing from absolute alcohol, the substance was obtained in the shape of little bundles, sometimes perfectly spherical, of poorly defined prisms, opaque, white, or yellowish in color, melting at  $226^{\circ}$ – $228^{\circ}$  and containing both sulphur and nitrogen.

*Action of Solvents.*—The substance is soluble in water, methyl, ethyl, isoamyl, propyl, and isobutyl alcohols; insoluble in ether, gasoline, benzene, and aceto-, propio-, and butyronitrils. In aqueous solution it is slightly acid to litmus but does not decompose carbonates.

*Action of Hydrochloric Acid.*—On boiling with concentrated hydrochloric acid the substance is completely converted into the acid ammonium salt of *o*-sulphobenzoic acid. To determine the amount formed, a weighed portion was treated with the acid, the solution evaporated to dryness, and the residue weighed.

| Weight substance. | Weight $\text{NH}_4$ salt obtained. | Calculated for 1 gram substance. |
|-------------------|-------------------------------------|----------------------------------|
| 0.1890            | 0.1681                              | 0.8894                           |
| 0.1147            | 0.1024                              | 0.8927                           |

One gram of saccharin on the same treatment should give 1.1912 grams of the salt.

The second of the two determinations given above was made on some of the compound obtained by Mathews.

*Action of Alkalies.*—On boiling with caustic potash, ammonia is evolved. To determine whether any amine was given off in this reaction the gas was passed into dilute hydrochloric acid, this solution evaporated to dryness, and the residue tested with caustic potash and chloroform. The odor of an isonitril was not obtained.

To determine whether an acetyl group was present in the molecule some of the substance was boiled with caustic alkali, the solution evaporated and treated with sulphuric acid and alcohol, but the odor of ethyl acetate was not detected.

Boiling with ammonia left the substance unchanged

Some was fused with caustic potash, the melt dissolved in water, acidified, and the solution extracted with chloroform. The chloroform, on evaporation, left a white residue giving a purple color with ferric chloride, and, on recrystallizing, it proved to be salicylic acid with a melting-point of  $155^{\circ}$ – $156^{\circ}$ . Saccharin also gives salicylic acid on fusion with alkali.

*Action of Phosphorus Pentachloride.*—0.4 gram of the substance was heated with 1 gram of phosphorus pentachloride to  $180^{\circ}$  for two hours. The product was poured on ice, where a yellow, oily material separated looking like *o*-sulphobenzodichloride and remaining liquid even on a freezing-mixture of ice and salt. Boiled with water, it went into solution, and, on evaporating, a slight residue was obtained which was not sweet. No ammonia was liberated on boiling the chloride with caustic alkali. On boiling it with ammonia and evaporating, a residue was obtained having an intensely sweet taste ; in all probability saccharin.

For purposes of comparison some pseudosaccharin chloride was prepared by the action of phosphorus pentachloride on saccharin ; the method of Jesurun.<sup>1</sup> One gram saccharin and 2.5 grams phosphorus pentachloride were heated to  $180^{\circ}$  for two hours. This mixture, poured on ice, gave a solid chloride crystallizing from benzene as found by Jesurun and melting at  $143^{\circ}$ – $144^{\circ}$ . It gives saccharin on simple boiling with water.

*Attempts to Form an Ester.*—The substance was dissolved in absolute alcohol and dry hydrochloric acid gas passed through the solution, keeping the latter cold. The first time this was tried some crystals separated looking like the acid ammonium salt of *o*-sulphobenzoic acid and having a high melting-point. On repeating the experiment using especial care to have anhydrous conditions, no crystals separated, and on evaporating the solution, the original substance (m. p.  $227^{\circ}$ – $228^{\circ}$ ) was reobtained unchanged.

<sup>1</sup> Ber. d. chem. Ges., 26, 2286.

The same want of success attended the use of zinc chloride as a dehydrating agent.

*Analysis.*—The following figures were obtained on analysis :

I. 0.1907 gram substance gave 0.3060 gram  $\text{CO}_2$ , and 0.0863 gram  $\text{H}_2\text{O}$ .

II. 0.2050 gram substance gave 0.3267 gram  $\text{CO}_2$ , and 0.0527 gram  $\text{H}_2\text{O}$ .

III. 0.1933 gram substance gave 0.3094 gram  $\text{CO}_2$ , and 0.0555 gram  $\text{H}_2\text{O}$ .

IV. 0.1924 gram substance gave 10.8 cc. nitrogen at  $22^\circ$ , and 760 mm. pressure.

V. 0.1890 gram substance gave 10.7 cc. nitrogen at  $23.5^\circ$ , and 756 mm. pressure.

VI. 0.2465 gram substance gave 0.2376 gram  $\text{BaSO}_4$ .

VII. 0.2195 gram substance gave 0.2120 gram  $\text{BaSO}_4$ .

|           | C.    | H.   | N.   | S.    |
|-----------|-------|------|------|-------|
| I .....   | 43.76 | 5.03 | .... | ....  |
| II .....  | 43.46 | 2.86 | .... | ....  |
| III ..... | 43.65 | 3.19 | .... | ....  |
| IV .....  | ....  | .... | 6.35 | ....  |
| V .....   | ....  | .... | 6.33 | ....  |
| VI .....  | ....  | .... | .... | 13.24 |
| VII ..... | ....  | .... | .... | 13.27 |

The compound is obviously no isomer of saccharin as the figures for these would be :

|         | Per cent. |
|---------|-----------|
| C ..... | 45.90     |
| H ..... | 2.73      |
| N ..... | 7.65      |
| S ..... | 17.49     |

The results correspond approximately to an empirical formula of  $\text{C}_9\text{H}_7\text{NSO}_5$ .

|         | Analysis.<br>Per cent. | Theory for $\text{C}_9\text{H}_7\text{NSO}_5$ .<br>Per cent. |
|---------|------------------------|--------------------------------------------------------------|
| C ..... | 43.62                  | 44.81                                                        |
| H ..... | 3.03                   | 2.90                                                         |
| N ..... | 6.34                   | 5.80                                                         |
| S ..... | 13.26                  | 13.27                                                        |



*b. Action of Propio- and Butyronitrils on o-Sulphobenzoic Acid.*  
 —Tubes were prepared containing equal molecules of the acid, and either propio- or butyronitril. They were heated to 165°–170° for three hours. At the end of this time the contents had an appearance precisely similar to that of the tubes containing acetonitril. They were treated in the same way as the latter, *i. e.*, extracted with absolute alcohol, leaving some acid ammonium salt of the acid undissolved, and the solution bone-blackened and evaporated to small bulk. On standing in a desiccator crystals separated, which, on removal from the brown syrupy liquid surrounding them, were found to be the same as those obtained by the action of acetonitril. This identity of product shows that the acetyl, propionyl, or butyryl group is not present as such in the molecule of the substance obtained.

## PART II.

### THE ACTION OF NITRILS ON BROM-, NITRO-, AND AMIDOBENZOIC ACIDS.

#### INTRODUCTION.

The following experiments were begun chiefly with the object of determining what influence the position of the substituting group, with reference to the carboxyl, had on the course of the reaction usual between aromatic acids and aliphatic nitrils, *i. e.*, the formation of aromatic nitrils and fatty acids.

The acids worked with were the brom-, nitro-, and amidobenzoic acids, and, of these, the three brom-, and the three nitro-, acids were successfully converted into their nitrils by heating under pressure with acetonitril, but, as the yield in each case was small, without any marked differences, no definite conclusions could be drawn as to what influence the relative position of the brom- and nitro- groups, respectively, had exerted.

On treating orthoamidobenzoic or anthranilic acid in the same way, no nitril at all was obtained but, instead, a very good yield of 2-methyl-4-ketodihydroquinazoline. The fact that no nitril is obtained was already shown by Mathews.<sup>1</sup>

<sup>1</sup> J. Am. Chem. Soc., 20, 654.

The discussion of this reaction together with other experiments with anthranilic acid will be found under its own heading.

#### EXPERIMENTAL WORK.

##### *Orthonitrobenzoic Acid and Acetonitril.*

Two tubes were prepared containing equal molecular proportions of acid and nitril. They were heated to  $220^{\circ}$ – $230^{\circ}$  for six hours. There was a slight pressure, and an odor of acetic acid, and the contents consisted of a dark-brown liquid. This was extracted with sodium carbonate solution, leaving a solid residue. The extract, on acidifying with hydrochloric acid, gave a precipitate, which, on recrystallizing, was found to be unchanged orthonitrobenzoic acid, melting at  $147^{\circ}$ – $150^{\circ}$ .

The residue left after the alkaline extraction was treated with hot water and this solution, on cooling, deposited needles having a melting-point of  $107^{\circ}$ – $108^{\circ}$ , and giving ammonia with caustic alkali. This agrees with the properties of *o*-nitrobenzonitril prepared by Baerthlein<sup>1</sup> by heating the amide with phosphorus pentoxide. He found its melting-point to be  $109^{\circ}$ .

Two other tubes were prepared containing 2 molecules of nitril to 1 of acid and heated to  $220^{\circ}$ – $230^{\circ}$  for six and twelve hours respectively. The first showed a slight pressure, and the second considerable. The contents of both consisted of a dark-brown liquid, and this was treated exactly as in the other two cases. No difference of any moment was noticed in the yield of nitril.

Besides the nitril another body was found in two of the above tubes. The residue from which the nitril had been removed by hot water was treated with hot alcohol, and a substance obtained crystallizing in needles and melting at  $222^{\circ}$ – $224^{\circ}$ . It is unchanged by boiling with hydrochloric acid, but with caustic potash it evolves ammonia, and, on acidifying the solution, extracting with ether, and recrystallizing the extract from water, a substance is obtained melting at  $139^{\circ}$ – $141^{\circ}$ ; probably *o*-nitrobenzoic acid.

<sup>1</sup> Ber. d. chem. Ges., 10, 1713.

Not enough of the first product was obtained for analysis ; it may be a secondary amide.

*Metanitrobenzoic Acid and Acetonitrile.*

*Tube 1.*—A tube containing the acid and nitril in equal molecular proportions was heated to  $250^{\circ}$ – $255^{\circ}$  for six hours. There was a slight pressure on opening, and the contents were black, with considerable liquid, and smelling of acetic acid. On extracting with sodium carbonate a residue was left consisting of carbonaceous matter mixed with some light-colored powder. The alkaline extract, on acidifying, gave a yellow precipitate which was found to be *m*-nitrobenzoic acid, melting, after two to three recrystallizations from water, at  $140^{\circ}$ – $141^{\circ}$ .

The residue was extracted with alcohol, which dissolved all but the carbonaceous matter. This solution, on evaporation, deposited a granular yellow precipitate which began to melt at  $105^{\circ}$ , but was not completely fused until  $130^{\circ}$ – $140^{\circ}$  were reached, showing that it was probably a mixture of the nitril and acid. Some of this precipitate was distilled and a colorless distillate obtained, which solidified to a crystalline mass, and, on crystallization from alcohol, gave long needles melting at  $117^{\circ}$ – $118^{\circ}$ . Some more, crystallized from water, melted at  $116^{\circ}$ – $117^{\circ}$ . This substance gave ammonia with caustic alkali, and, on boiling with hydrochloric acid, evaporating, and recrystallizing, *m*-nitrobenzoic acid with a melting-point of  $135^{\circ}$ – $137^{\circ}$  was obtained.

Engler<sup>1</sup> and Fricke<sup>2</sup> found the melting-point of *m*-nitrobenzonitril to be  $115^{\circ}$ , while Beilstein and Kuhlberg<sup>3</sup> give it as  $117^{\circ}$ – $118^{\circ}$ .

*Tube 2.*—This contained the same charge as No. 1, but was heated first to  $220^{\circ}$ – $230^{\circ}$  for twelve hours, and then to  $250^{\circ}$ – $255^{\circ}$  for four and one-half hours. There was now a slight pressure, and the contents consisted entirely of a very dark-colored liquid. This was treated with soda solution like the first tube and much unchanged acid recovered. The residue

<sup>1</sup> Ann. Chem. (Liebig), 149, 297.

<sup>2</sup> Ber. d. chem. Ges., 7, 1321.

<sup>3</sup> Ann. Chem. (Liebig), 146, 336.

again consisted of tarry material mixed with a light powder, and this, on extraction with hot water, without previous distillation, yielded some more of the nitril, melting at  $114^{\circ}$ – $115^{\circ}$ .

*Paranitrobenzoic Acid and Acetonitril.*

A tube was prepared containing the nitril and acid in the proportion of 4 molecules of the former to 1 molecule of the latter. This quantity of nitril was used because of the extreme lightness of *p*-nitrobenzoic acid and the difficulty of adequately moistening it with less. In my subsequent work I continued using an excess of nitril in such cases, the excess being recovered by distillation before any further work was done on the tube-contents.

The above tube was heated to  $250^{\circ}$ – $260^{\circ}$  for six hours. There was no pressure and the contents were crystalline. After distilling off the excess of acetonitril, the residue smelt strongly of acetic acid. It was treated with soda solution and unchanged acid recovered. It was then extracted with hot water, and this solution, on cooling, deposited yellow needles with a melting-point, after two recrystallizations from dilute alcohol, of  $145^{\circ}$ – $149^{\circ}$ . This substance evolved ammonia on boiling with caustic alkali, and from the solution, on acidifying, *p*-nitrobenzoic acid, with a melting-point of  $235^{\circ}$ – $236^{\circ}$ , was obtained.

The melting-point of *p*-nitrobenzonitril is given as  $147^{\circ}$  by Fricke,<sup>1</sup> and this is confirmed by Sandmeyer.<sup>2</sup>

*Orthobrombenzoic Acid and Acetonitril.*—The acid was heated with excess of nitril to  $150^{\circ}$ – $160^{\circ}$  for five hours, then to  $200^{\circ}$ – $210^{\circ}$  for six hours, and finally to  $230^{\circ}$ – $240^{\circ}$  for five and one-half hours. There was no pressure and the contents were crystalline. After distilling off the excess of nitril, the product was treated with soda solution, and the residue distilled with steam, giving white needle-like crystals, melting at  $51^{\circ}$ , in the distillate. Schöpf<sup>3</sup> gives the melting-point of *o*-brombenzoic acid as  $51^{\circ}$ .

<sup>1</sup> Ber. d. chem. Ges., 7, 1322.

<sup>2</sup> *Ibid.*, 18, 1492.

<sup>3</sup> *Ibid.*, 23, 3436.



No more *o*-brombenzoic acid being available this experiment could not be repeated and a sufficient amount of the nitril obtained for further tests, but, as both the meta and para acids give the corresponding nitrils, as shown below, there is no reason for supposing that the product was not *o*-brombenzonitril.

*Metabrombenzonitril and Acetonitril.*—A tube containing 4 grams of the acid and 11 grams of nitril was heated to  $200^{\circ}$ – $210^{\circ}$  for three hours. As the contents appeared unchanged and did not become liquid on the water-bath, though the nitril melts at  $38^{\circ}$ , the tube was resealed and heated to  $225^{\circ}$ – $230^{\circ}$  for six hours. There was no pressure and the contents consisted of a mobile-brown liquid with a very small amount of black solid matter in suspension. The excess of acetonitril having been distilled off, the residue remained fluid on the water-bath but solidified on cooling. It was extracted with soda solution and some unchanged *m*-brombenzoic acid recovered. The residue was dissolved in ether, the solution filtered, and evaporated in a desiccator. A white crystalline body was thus obtained, having a melting-point of  $38^{\circ}$ – $39^{\circ}$ . On boiling it with caustic alkali, ammonia was evolved, and, on acidifying, *m*-brombenzoic acid, with a melting-point of  $150^{\circ}$ – $151^{\circ}$ , was obtained.

Engler<sup>1</sup> first made *m*-brombenzonitril and found its melting-point to be  $38^{\circ}$ . This has been confirmed by Schöpff<sup>2</sup> and Sandmeyer.<sup>3</sup>

*Parabrombenzoic Acid and Acetonitril.*—Equal molecular proportions of the acid and nitril were heated to  $150^{\circ}$ – $160^{\circ}$  for five hours, then to  $200^{\circ}$ – $210^{\circ}$  for six hours, and finally to  $235^{\circ}$ – $240^{\circ}$  for five and a half hours. There was no pressure and a strong odor of acetic acid. The contents were dark-colored and crystalline, wet by a brown liquid. They were extracted with soda solution, as usual, and the residue distilled with steam, giving long colorless crystals in the distillate. These, recrystallized from dilute alcohol, melted at  $112^{\circ}$ – $113^{\circ}$ . The aqueous residue in the distillation flask, on cooling, deposited

<sup>1</sup> Ber. d. chem. Ges., 4, 708.

<sup>2</sup> *Ibid.*, 23, 3437.

<sup>3</sup> *Ibid.*, 18, 1495.

crystals of *p*-brombenzoic acid with a melting-point of 249°–250°.

Schöpf<sup>1</sup> found the melting-point of *p*-brombenzonitril to be 113°.

## THE ACTION OF NITRILS ON ANTHRANILIC ACID.

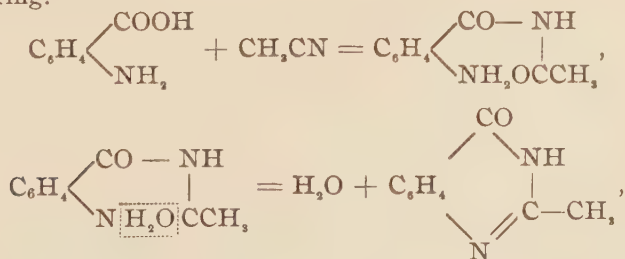
### INTRODUCTION.

The action of acetonitril on anthranilic acid under pressure was first studied by Mathews.<sup>2</sup> He found that a crystalline substance was formed melting at 232° and giving, on boiling with concentrated hydrochloric acid, a body crystallizing in long needles and subliming without melting. These products were not identified.

I have repeated these experiments and find that the substance formed in the tube is the 2-methyl-4-ketodihydroquinazoline, first prepared by Weddige,<sup>3</sup> which, with hydrochloric acid, gives the HCl salt. As this is the first quinazoline derivative to be made by the action of a nitril it opens up an interesting field for further investigation.

In the same manner the action of propionitril on anthranilic acid gives 2-ethylquinazolone; benzonitril, 2-phenyl; benzylcyanide, 2-benzyl; and paratolunitril, 2-paratolyl. These are all the derivatives thus far made by this method. The yields are quite good and the compounds are easily purified.

The reaction which takes place is probably first the formation of a secondary amide which then loses water, thus closing the ring.

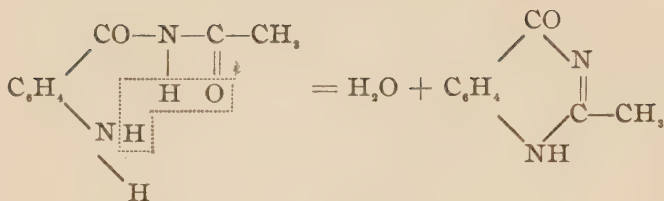


or

<sup>1</sup> Ber. d. chem. Ges., 23, 3437.

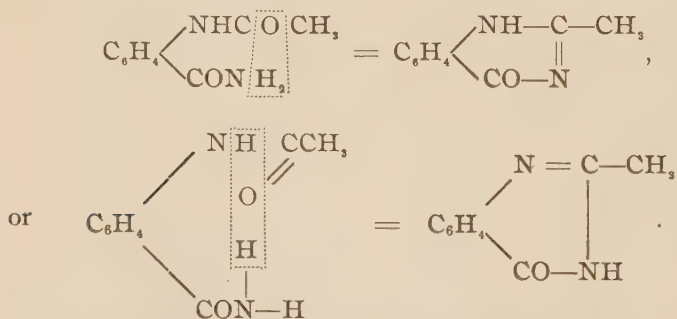
<sup>2</sup> J. Am. Chem. Soc., 20, 654.

<sup>3</sup> J. prakt. Chem. (2), 31, 124.



Whether this is the course of the reaction is as yet unproved and forms the subject of further research already begun. The probability of the formation of the secondary amide is indicated by the work of Gautier<sup>1</sup> and of Colby and Dodge,<sup>2</sup> who very often found such an amide to be the product of the action of nitrils on acids.

An interesting question which arises in the study of these compounds is one regarding the manner in which the water is eliminated, for, as shown by the equations, this may happen in two ways, giving rise to two different compounds according as the double bond is at 2 or 3. According to whichever way Weddige's<sup>3</sup> reaction proceeds, the methyl quinazolone produced by the new synthesis ought to differ from his if the water is eliminated in a similar manner. Equations will show this clearly. Weddige's reactions are as follows :

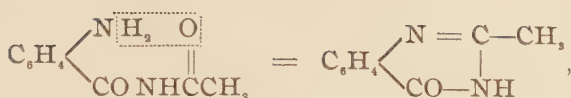


Similar condensations in the nitril reaction would lead to the following :

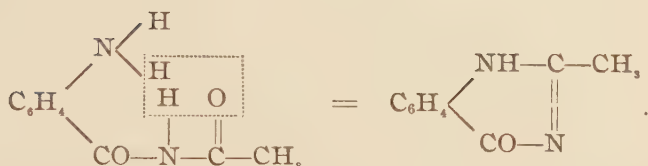
<sup>1</sup> Compt. rend., (1868), 67, 1255.

<sup>2</sup> Am. Chem. J., 13, 1.

<sup>3</sup> J. prakt. Chem. (2), 31, 124.



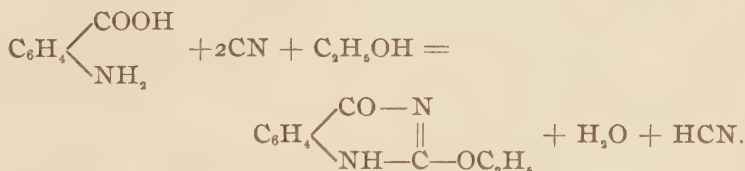
and



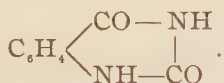
The difference between these two compounds would, of course, be slight.

#### HISTORICAL.

The first quinazoline derivative prepared was ethoxydihydroketoquinazoline made by Peter Griess,<sup>1</sup> in 1869, by the action of cyanogen on anthranilic acid in alcoholic solution :



This compound, on boiling with hydrochloric acid, gives diketotetrahydroquinazoline or benzoylene urea :



The most important syntheses that have been discovered since are the following :

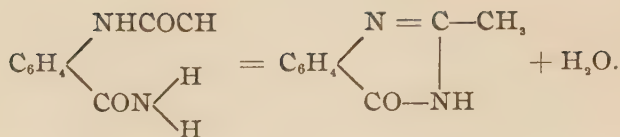
Weddige<sup>2</sup> and Körner<sup>3</sup> found that acyl-*o*-amidobenzamides, on boiling in aqueous solution, or heating above their melting-points, split off water and formed ketodihydroquinazolines.

<sup>1</sup> Ber. d. chem. Ges., 2, 415.

<sup>2</sup> J. prakt. Chem. (2), 31, 124.

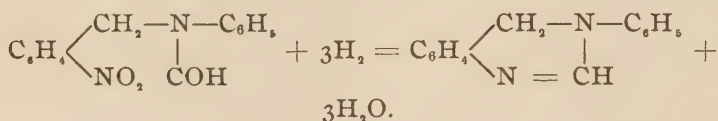
<sup>3</sup> *Ibid.* (2), 36, 155.





Weddige also obtained the same bodies by treating the acylamidobenzoic acid ethyl esters with aqueous ammonia.

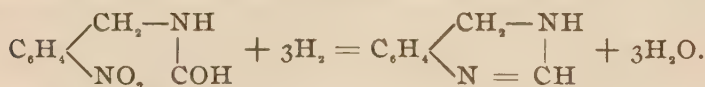
Paal and Busch,<sup>1</sup> by the reduction of acyl-*o*-nitrobenzylanilides, obtained dihydroquinazolines :



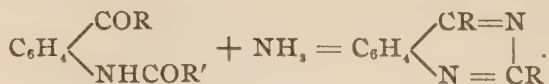
These were the first quinazolines free of oxygen prepared.

This particular reaction was also investigated by Söderbaum and Widmann<sup>2</sup> with very interesting results. They noted a number of cases in which the closing of the ring could not be effected.

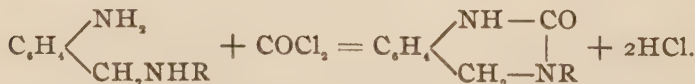
Dihydroquinazoline itself was first prepared by Gabriel and Jansen<sup>3</sup> by the reduction of *o*-nitrobenzylformamide :



Bischler<sup>4</sup> obtained quinazoline derivatives by the action of ammonia on acyl-*o*-amidobenzoic acids, aldehydes, and ketones :



Some more ketotetrahydroquinazolines were prepared by Busch<sup>5</sup> by treating *o*-amidobenzylamine, aniline, etc., with phosgene :



<sup>1</sup> Ber. d. chem. Ges., **22**, 2683.

<sup>2</sup> *Ibid.*, **23**, 2187.

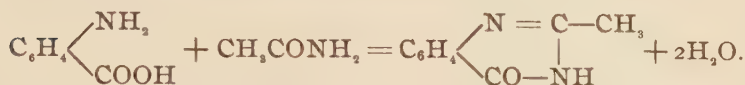
<sup>3</sup> *Ibid.*, **23**, 2814.

<sup>4</sup> *Ibid.*, **24**, 506.

<sup>5</sup> *Ibid.*, **25**, 2853.

The corresponding thio derivatives were prepared by using carbon disulphide.

One of the most recent syntheses is that of Numentowski,<sup>1</sup> which consists in heating anthranilic acid with amides :



#### EXPERIMENTAL WORK.

##### *Preparation of 2-Methyl-4-ketodihydroquinazoline.*

Anthranilic acid was heated with an excess of acetonitril (sufficient to thoroughly wet the acid) in a sealed tube to 200°–210° for six hours. There was considerable pressure of carbon dioxide on opening and the contents consisted of a felted crystalline mass wet by a dark liquid. The excess of acetonitril was distilled off and the residue, after washing with a small quantity of ether, was crystallized from hot water, and decolorized with bone-black. Usually one such crystallization was sufficient to give a pure product melting at 231°–232°.

On analysis this gave the following figures :

I. 0.1634 gram substance gave 0.3973 gram CO<sub>2</sub>, and 0.0726 gram H<sub>2</sub>O.

II. 0.1582 gram substance gave 0.3904 gram CO<sub>2</sub>, and 0.0711 gram H<sub>2</sub>O.

III. 0.1584 gram substance gave 0.3898 gram CO<sub>2</sub>, and 0.0722 gram H<sub>2</sub>O.

IV. 0.1466 gram substance gave 0.3628 gram CO<sub>2</sub>, and 0.0666 gram H<sub>2</sub>O.

V. 0.1633 gram substance gave 27 cc. N at 25° and 756 mm. pressure.

VI. 0.1613 gram substance gave 26 cc. N at 24° and 756 mm. pressure.

VII. 0.1468 gram substance gave 23.8 cc. N at 22.5° and 750 mm. pressure.

<sup>1</sup> J. prakt. Chem. (2), 51, 564.

|                               | C.    | H.   | N.    |
|-------------------------------|-------|------|-------|
| I.....                        | 66.31 | 4.94 | ....  |
| II.....                       | 67.3  | 4.99 | ....  |
| III.....                      | 67.11 | 5.06 | ....  |
| IV.....                       | 67.49 | 5.04 | ....  |
| V.....                        | ....  | .... | 18.33 |
| VI.....                       | ....  | .... | 17.97 |
| VII.....                      | ....  | .... | 18.07 |
| Theory for $C_9H_8N_2O$ ..... | 67.50 | 5.00 | 17.50 |

The nitrogen percentages, for some unknown reason, were always too high, but check analyses run with known substances were too high by the same amounts.

The *nitric and chromic acid salts* of this quinazolon were prepared and found to differ somewhat in their action toward heat from the salts obtained by Niementowski,<sup>1</sup> who worked with Weddige's product. The nitric acid salt decomposed at 187° instead of at 195°, and the chromic acid salt blackened at about 176° instead of at 182°. The chromic salt, on analysis, was found to contain 19.41 per cent. chromium, while theory ( $C_9H_8N_2O.CrO_3$ ) demands 20 per cent., a result agreeing very well with Niementowski's.

The *platinic chloride double salt* crystallized from hot water in coarse red crystals, as described by Weddige.<sup>2</sup> The percentage of platinum was determined by ignition.

|         | Theory for<br>( $C_9H_8N_2O.HCl$ ) <sub>2</sub> PtCl <sub>4</sub> . | Found. |       |
|---------|---------------------------------------------------------------------|--------|-------|
|         |                                                                     | I.     | II.   |
| Pt..... | 26.61                                                               | 26.62  | 26.78 |

The *methyl ether* was prepared by heating the methyl quinazolon with methyl iodide and caustic potash in alcoholic solution. On evaporating the alcohol and recrystallizing the residue from water, white needles were obtained melting at 69° in the hydrated condition and at 110°–112° when anhydrous.

For purposes of comparison some 2-methyl-4-ketodihydroquinazoline was prepared by Bischler's<sup>3</sup> method from the ammonium salt of anthranilic acid. The salt is melted, kept at the boiling-point for some time, and the product recrystal-

<sup>1</sup> Ber. d. chem. Ges., 29, 1360.

<sup>2</sup> J. prakt. Chem. (2), 36, 141.

<sup>3</sup> Ber. d. chem. Ges., 26, 1349.

lized from water. The quinazolon thus prepared agreed in all its properties with that obtained by me. The chromic and nitric acid salts and the methyl ether were also prepared and found identical.

*By-products.*—The ether used for washing the crystals, *vid.* method of preparation, on evaporating, gave a tarry residue smelling of aniline. On distilling with steam the aniline was obtained in the distillate and gave the characteristic purple color with a solution of bleaching-powder.

Some of the ether residue, on standing, deposited long colorless plates which were mechanically separated and recrystallized from benzol. This substance was identified as acetanilid, melting at 115°–117° and giving aniline on boiling with hydrochloric acid.

The addition of acetic anhydride to the tube-charges caused a great improvement in the yield and purity of the quinazolon. When almost enough anhydride was added to take up all the water liberated the yield was doubled and brought up to 45 per cent. of the theoretical, while the tube contents were very light-colored with no tar whatever.

*2-Ethyl-4-ketodihydroquinazoline,*

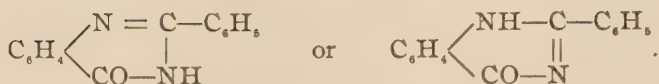


Anthranilic acid and excess of propionitril were heated to 200°–210° for six hours. On opening there was much pressure, but the contents were crystalline. The small amount of liquid present was drained off and the residue crystallized from dilute alcohol. The compound forms needles sometimes united to nodules and melts at 226°–227°. It has already been made by Bischler and Lang<sup>1</sup> by the oxidation of 2-ethylquinazoline with chromic acid. They found its melting-point to be 227°–228°, while Niementowski,<sup>2</sup> making it from anthranilic acid and propionamid, found it to melt at 225°.

<sup>1</sup> Ber. d. chem. Ges., 28, 284.

<sup>2</sup> J. prakt. Chem. (2), 51, 568.



*2-Phenyl-4-ketodihydroquinazoline,*

Anthranilic acid and benzonitril were heated to 200°–210° for six hours. There was much pressure in the tube and the contents were black. The liquid was filtered off and the solid recrystallized from absolute alcohol. It forms small yellow needles and can be obtained colorless by sublimation, when it melts at 228°–229°.

Körner<sup>1</sup> prepared this derivative by heating benzoyl-*o*-amido-benzamide. He states its melting-point to be 233°–234°.

*2-Benzyl-4-ketodihydroquinazoline.*—On heating anthranilic acid with benzyl cyanide to 200°–210° for five hours, a light-brown crystalline product was obtained. Recrystallization from alcohol gave very small needles melting at 246°–247°.

*2-p-Tolyl-4-ketodihydroquinazoline.*—*p*-Tolunitril was heated with anthranilic acid to 200°–210° for five hours. There was considerable pressure on opening and the contents consisted of needle-like crystals in a black liquid. On recrystallizing from alcohol the quinazolone was obtained pure, melting at 236°.

The last two substances are new. They have not yet been analyzed because the time has been given to a study of the general reaction.

## SUMMARY.

I. The action of acetonitril on  $\beta$ -sulphopropionic acid yields practically no definite compound.

II. *o*-Sulphobenzoic acid heated with nitrils does not give saccharin nor an isomer of saccharin, but another body having an empirical formula of  $\text{C}_9\text{H}_7\text{NSO}_6$ .

III. The three brom- and the three nitrobenzoic acids can be partly converted into their nitrils by the action of acetonitril.

IV. The action of nitrils, both aliphatic and aromatic, on anthranilic acid causes the formation of quinazolone derivatives.

In concluding, I wish to express my gratitude to Mr. Marston T. Bogert, my instructor, for the assistance rendered me in the course of this work.

<sup>1</sup> J. prakt. Chem. (2), 36, 155.

### BIOGRAPHICAL.

August Henry Gotthelf graduated from Columbia Grammar School, in New York City, in 1893, entered the School of Mines of Columbia College, and graduated from that institution in 1897 with the degree of Bachelor of Science. He obtained the degree of Master of Arts from Columbia University in 1898.

He has participated in the publication of the following papers :

“ The Theory of the Formation of Nickel Sulphide ” (with J. L. R. Morgan). *J. Am. Chem. Soc.*, **21**, 494.

“ A New Synthesis in the Quinazoline Group ” (with M. T. Bogert). *J. Am. Chem. Soc.*, **22**, 129.









